IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Michel PAIRET et al. :

Serial No.: 10/776,757 : Examiner: Barbara P. Badio

Filed: February 11, 2004 : Group Art Unit: 1628

For: PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS AND CORTICOSTEROIDS

BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 of the above-identified application. A Notice of Appeal was filed on August 19, 2010.

(i) REAL PARTY IN INTEREST

The real party in interest is Boehringer Ingelheim International GmbH.

(ii) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(iii) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66.
Claims allowed:	(none)
Claims canceled:	Claims 2, 5-8, 11-14, 18, 22, 24, 27-30, 38 and 40-62.
Claims withdrawn:	(none)
Claims on Appeal:	Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 (Copy of claims on appeal in attached Appendix).

(iv) STATUS OF AMENDMENTS

No amendments after the Final Rejection have been proposed by Appellants.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention (independent claim 1) is directed to an inhalable powder pharmaceutical composition (see, e.g., page 1, lines 16-23; page 3, lines 13-15; and page 8, lines 6-7; of the instant specification). The composition comprises: (a) a tiotropium salt or a hydrate thereof (see, e.g., page 2, lines 11-13; and page 3, lines 24-26; of the instant specification); (b) a steroid which is ciclesonide (see, e.g., page 2, line 28, to page 3, line 5; of the instant specification), and (c) a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose (see, e.g., page 3, line 30, to page 4, line 3; and page 8, lines 9-12; of the instant specification). The tiotropium salt and the steroid are optionally in the form of their enantiomers, mixtures of their enantiomers, or their racemates (see, e.g., page 4, lines 25-27, of the instant specification).

Appellants' invention (independent claim 39) is directed to a pharmaceutical composition consisting essentially of: (a) tiotropium salt (see, e.g., page 2, lines 11-13; and page 3, lines 24-26; of the instant specification); and (b) a steroid which is ciclesonide (see, e.g., page 2, line 28, to page 3, line 5; of the instant specification), wherein the pharmaceutical composition is in the form of an inhalable powder (see, e.g., page 1, lines 16-23; page 3, lines 13-15; and page 8, lines 6-7; of the instant specification).

Appellants' invention (independent claim 63) is directed to a kit comprising one or more unit dosage containers containing an inhalable powder pharmaceutical composition (see, e.g., original claim 63; page 1, lines 16-23; page 3, lines 13-15; and page 8, lines 6-7; of the instant specification). The composition comprises: (a) a tiotropium salt or a hydrate thereof (see, e.g., page 2, lines 11-13; and page 3, lines 24-26; of the instant specification); (b) a steroid which is ciclesonide (see, e.g., page 2, line 28, to page 3, line 5; of the instant specification), and a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose (see, e.g., page 3, line 30, to page 4, line 3; and page 8, lines 9-12; of the instant specification). The tiotropium salt and the steroid are optionally in the form of their enantiomers, mixtures of their enantiomers, or their racemates (see, e.g., page 4, lines 25-27, of the instant specification).

Appellants' invention (independent claim 65) is directed to a kit (see, e.g., original claim 65; page 1, lines 16-23; page 3, lines 13-15; and page 8, lines 6-7; of the instant

specification) comprising:

(a) a first container containing a first inhalable powder pharmaceutical formulation comprising a tiotropium salt (see, e.g., page 2, lines 11-13; page 3, lines 24-26; page 1, lines 16-23; page 3, lines 13-15; and page 8, lines 6-7; of the instant specification) and;

(b) a second container containing a second inhalable powder pharmaceutical formulation comprising a steroid which is ciclesonide (see, e.g., page 1, lines 16-23; page 2, line 28, to page 3, line 5; page 3, lines 13-15; and page 8, lines 6-7;),

each container further containing a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose (see, e.g., page 3, line 30, to page 4, line 3; and page 8, lines 9-12; of the instant specification).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following outstanding grounds of rejection are requested to be reviewed on appeal. For each ground, any separate consideration of the claims subject to that rejection is indicated.

1. The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66, on appeal, under 35 U.S.C. §103, as being obvious over the combination of Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163).

1a. Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37 and 63-66, on appeal, are grouped together.

1b. Claim 39, on appeal, is separately grouped together for the reasons given in the argument.

2. The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66, on appeal, under 35 U.S.C. §103, as being obvious over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163) in combination.

2a. Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37 and 63-66, on appeal, are grouped together.

2b. Claim 39, on appeal, is separately grouped together for the reasons given in the argument.

(vii) ARGUMENT

1a. Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37 and 63-66, on appeal, are not obvious to one of ordinary skill in the art over the combination of Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163); thus the rejection under 35 U.S.C. §103 based on these references should be reversed

Appellants urge that the combination of reference teachings fails to create a prima facie case for obviousness of the claimed invention, as discussed further below. Appellants also urge that the Declaration under 37 C.F.R. §1.132 (copy attached; see Evidence Appendix) provides further clear and convincing evidence of the nonobviousness of the claimed invention, as discussed immediately below.

The law is clear that a showing of synergism – alone – can be sufficient to prove nonobviousness. For example, MPEP §716.02(a)(I) and the decisions cited therein make clear that a showing of synergism alone can be sufficient proof of nonobviousness, stating:

> Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

The apparent position taken in the Final Office action is that a showing of synergism alone cannot prove nonobviousness because declarations under 37 C.F.R. §1.132 must compare the claimed invention and the closest prior art. Appellants urge that the quotation from the top of page 4 of the Final Office action is being taken out of context. The quotation pertains to the situation where applicant is providing a comparison to the prior art. If the evidence of unexpected results is from a comparison of the claimed invention and the prior art, then, yes, the prior art that is compared should be the closest prior art. However, this does not mean that clear and convincing evidence of nonobviousness cannot be provided in ways other than by direct comparison of the claimed invention with the closest prior art. To the contrary, the law and PTO practice make clear that there is more than one way to prove nonobviousness. See the *Merck* case cited above and also *In re Soni*, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), confirming that "all evidence of nonobviousness must be considered when assessing patentability" and finding nonobviousness based on data showing an unexpected advantage from a showing of properties rather than from a direct comparison of the prior art.

See also *American Hoist and Derrick Co. v. Sowa & Sons*, 220 USPQ 763, 771 (Fed. Cir. 1984), supporting that the existence of an unexpected result **or** a synergistic effect may support nonobviousness. Thus, while a direct comparison to the closest prior art composition (presumably the Nishimura composition since it is the only specific embodiment in the prior art which combines two actives) is one way to prove nonobviousness, the absence of such a direct comparison does not preclude appellants from proving nonobviousness in other ways, i.e., with the showing of synergism. Appellants urge that the clear and convincing showing of an unexpected synergistic effect of their combination in the 37 C.F.R. §1.132 declaration is sufficient to prove nonobviousness.

The instant claims on appeal all have the aspect of a very specific combination of a tiotropium salt and the specific steroid ciclesonide. The declaration provides a side-by-side comparison of the bronchoprotective effect achieved by this specific combination according to the invention versus the additive effect of the two components separately. The results show the surprising effect that the combination over a 24 hour period is more than twice as effective as the added results of the two components individually. Thus, a very high degree of synergism is demonstrated.

The declaration shows that the bronchoprotective effect of the ciclesonide (0.1 mg/kg) was 5% at 3 hours and 5% at 24 hours and the bronchoprotective effect of the tiotropium bromide (0.06 mg/kg) was 35% at 3 hours and 12% at 24 hours. The additive effects of the components individually were thus 40% at three hours and 17% at 24 hours. The combination according to the invention, however, provided bronchoprotection of 49% at 3 hours and 41% at 24 hours. Thus, the sustained bronchoprotection effect over 24 hours for the claimed combination was **more than twice** that of the added effect of the two components separately. This is a highly significant advantage.

That the unexpected synergistic effect is highly significant should be self-evident from the data and from its graphic presentation in the graph attached to the declaration. The advantage achieved is also a highly practical advantage. It should be self-evident that the observed surprising bronchoprotective effect is highly practical for using the combination in treating respiratory conditions. The highly synergistic effect over a 24 hour period is of a particularly practical advantage. The specification as a whole supports that the bronchoprotective activity makes the compounds useful for treating inflammatory or obstructive diseases of the respiratory tract; see, e.g., page 1, lines 16-23, and page 4, lines 5-13, of the instant specification. The PTO has provided no evidence or reasoning to suggest that the advantages shown by appellants' are not significant or practical.

It is alleged in the Final Office action (page 4, second paragraph) that the comparison is improperly made of results obtained in humans (apparently referring to Nishimura) with results obtained in laboratory animals (dogs in appellants' data). This allegation is factually incorrect. The showing of synergism in the declaration is based only on appellants' own data from experiments with dogs. The comparison is of the combination composition according to the invention versus the additive effect of the components separately. This is the classic way of showing synergism. Appellants never alleged any comparison to Nishimura. Appellants arguments regarding Nishimura (as detailed below) pertain to the fact that it fails to suggest that its combination would provide a synergistic effect and, thus, appellants showing is unexpected in view of Nishimura.

The record is believed to make clear that the significant and practical synergistic advantage shown for appellants' combination is unexpected from the cited prior art. There are no teachings in the prior art from which one of ordinary skill in the art would expect that the combination of tiotropium and ciclesonide could provide an effect significantly greater than the additive effect of the components individually, certainly not more than twice the additive effect. The teachings of Nishimura regarding its oxitropium/beclamethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclamethasone provided only a "small improvement" in treatment; see the concluding discussion on pg. 87. Further, the title of Nishimura points only to an "additive effect" from the combination. Appellants object to the allegation in the Final Office action (page 3) that applicants admitted that Nishimura shows synergism. Appellants never made any such admission. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

It is alleged in the Final Office action (page 3, last sentence) that appellants' showing is not persuasive "because it does not show the results are greater than those expected from the prior art." Appellants strongly disagree. Appellants have shown that the 24 hour sustained bronchoprotection effect for the claimed combination was **more than twice** that of the added effect of the two components separately. This is clearly unexpected over the Nishimura teachings. From Nishimura and the other references, one of ordinary skill in the art could not have expected more than just an additive effect from a combination of anticholinergic and steroid. Appellants show an effect more than double the additive effect. Appellants are at a loss as to how one could conclude from the cited references that such a dramatic synergistic advantage could have been expected. It is true that Nishimura teaches

combining oxitropium bromide and beclomethasone (just this specific combination). But neither this teaching, nor the teachings in Banholzer, give any hint that the combination of the different anticholinergic, tiotropium, and different steroid, ciclesonide, would provide a significantly higher than additive effect. This synergistic effect is unquestionably unexpected.

Considering the record as a whole, appellants urge that they have provided clear and convincing evidence of significant and practical advantages of their particular combination. Further, they have shown that these advantages were unexpected in view of the prior art teachings. The prior art gives no hint to one of ordinary skill in the art that the specific combination of the specific anticholinergic, tiotropium salt, and the specific corticosteroid, ciclesonide, would be particularly advantageous. Thus, a clear and convincing showing of nonobviousness is provided by the showing of synergism. In view of the narrow claim scope – i.e., combination of two specific actives – the showing is also commensurate in scope with the claimed invention. Appellants urge that the showing of nonobviousness alone provides sufficient basis to reverse the obviousness rejection.

Further, appellants submit that the cited references considered as a whole fail to establish a prima facie case of obviousness or, at most, only a weak case which is readily overcome by the showing of nonobviousness in the declaration.

Nishimura discloses the use of a particular combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone diproprionate, for use in treating chronic asthma; see, e.g., the Abstract. Nishimura indicates that the combination of the oxitropium bromide provided advantages when administered in addition to beclomethasone diproprionate. But the advantages are only minor and there is no allegation or proof that the advantages are more than merely the additive effect. The title of the Nishimura article refers to only an "additive effect" from the oxitropium bromide.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts; see, e.g., col. 1, lines 15-58. Claim 5 is directed particularly to tiotropium salts.

The apparent basis for the rejection is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide of Nishimura with the tiotropium compound disclosed in Banholzer. However, such a combination would not meet or suggest the elements of the claims and, thus, not support a prima facie case of obviousness. The instant claims recite a combination of the tiotropium compound and the particular steroid, ciclesonide. Neither of Nishimura or Banholzer provide any suggestion to combine the

particular steroid ciclesonide. Nishimura discloses only a beclomethasone salt. Banholzer provides no teachings regarding any steroid. The combined reference teachings thus fail to meet this claim element.

Also, the Final Office action provides no articulated reasoning with a rationale underpinning as to why one of ordinary skill in the art would have reason to make the specific combination of the claimed elements. The Final Office action provides the mere conclusory statement that the two actives were known, thus, it would be obvious to combine them. The Supreme Court has cautioned against use of this conclusory type of reasonsing to support an obviousness rejection; see, KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385, at 1396 (2007), stating: "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." As further stated in KSR "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."

The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose." Neither of Nishimura and Banholzer provide any teaching regarding a composition containing such particular excipient with the particular combination of tiotropium and ciclesonide.

For these additional reasons, i.e., the weakness of the prima facie showing, the combined references in view of the evidence of nonobviousness fail to support the obviousness rejection. It is urged that the cited prior art, considered as a whole and in view o of the evidence of unexpected results, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

1b. Claim 39, on appeal, is not obvious to one of ordinary skill in the art over the combination of Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163); thus the rejection under 35 U.S.C. §103 based on these references should be reversed

The additional distinction of the claims discussed in Issue **1a.** regarding the failure of the references to disclose or suggest a composition with "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose" does not apply to claim 39. However, all of the other arguments made in Issue **1a.**

above apply and are incorporated by reference herein. Those arguments which apply – and which are the primary arguments for distinguishing the claimed invention – are sufficient to support the nonobviousness of claim 39. Thus, the rejection under 35 U.S.C. §103 of claim 39, on appeal, should also be reversed.

2a. Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37 and 63-66, on appeal, are not obvious to one of ordinary skill in the art over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163) in combination; thus, the rejection under 35 U.S.C. §103 based on these references should be reversed

Appellants urge that the combination of reference teachings fails to create a prima facie case for obviousness of the claimed invention, as discussed further below. Appellants also urge that the Declaration under 37 C.F.R. §1.132 (copy attached; see Evidence Appendix) provides further clear and convincing evidence of the nonobviousness of the claimed invention, as discussed immediately below.

The law is clear that a showing of synergism – alone – can be sufficient to prove nonobviousness. For example, MPEP §716.02(a)(I) and the decisions cited therein make clear that a showing of synergism alone can be sufficient proof of nonobviousness, stating:

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(Fed. Cir. 1995), confirming that "all evidence of nonobviousness must be considered when assessing patentability" and finding nonobviousness based on data showing an unexpected advantage from a showing of properties rather than from a direct comparison of the prior art. See also *American Hoist and Derrick Co. v. Sowa & Sons*, 220 USPQ 763, 771 (Fed. Cir. 1984), supporting that the existence of an unexpected result **or** a synergistic effect may support nonobviousness. Thus, while a direct comparison to the closest prior art composition (presumably the Nishimura composition since it is the only specific embodiment in the prior art which combines two actives) is one way to prove nonobviousness, the absence of such a direct comparison does not preclude appellants from proving nonobviousness in other ways, i.e., with the showing of synergism. Appellants urge that the clear and convincing showing of an unexpected synergistic effect of their combination in the 37 C.F.R. §1.132 declaration is sufficient to prove nonobviousness.

The instant claims on appeal all have the aspect of a very specific combination of a tiotropium salt and the specific steroid ciclesonide. The declaration provides a side-by-side comparison of the bronchoprotective effect achieved by this specific combination according to the invention versus the additive effect of the two components separately. The results show the surprising effect that the combination over a 24 hour period is more than twice as effective as the added results of the two components individually. Thus, a very high degree of synergism is demonstrated.

The declaration shows that the bronchoprotective effect of the ciclesonide (0.1 mg/kg) was 5% at 3 hours and 5% at 24 hours and the bronchoprotective effect of the tiotropium bromide (0.06 mg/kg) was 35% at 3 hours and 12% at 24 hours. The additive effects of the components individually were thus 40% at three hours and 17% at 24 hours. The combination according to the invention, however, provided bronchoprotection of 49% at 3 hours and 41% at 24 hours. Thus, the sustained bronchoprotection effect over 24 hours for the claimed combination was **more than twice** that of the added effect of the two components separately. This is a highly significant advantage.

That the unexpected synergistic effect is highly significant should be self-evident from the data and from its graphic presentation in the graph attached to the declaration. The advantage achieved is also a highly practical advantage. It should be self-evident that the observed surprising bronchoprotective effect is highly practical for using the combination in treating respiratory conditions. The highly synergistic effect over a 24 hour period is of a particularly practical advantage. The specification as a whole supports that the bronchoprotective activity makes the compounds useful for treating inflammatory or

obstructive diseases of the respiratory tract; see, e.g., page 1, lines 16-23, and page 4, lines 5-13, of the instant specification. The PTO has provided no evidence or reasoning to suggest that the advantages shown by appellants' are not significant or practical.

It is alleged in the Final Office action (page 4, second paragraph) that the comparison is improperly made of results obtained in humans (apparently referring to Nishimura) with results obtained in laboratory animals (dogs in appellants' data). This allegation is factually incorrect. The showing of synergism in the declaration is based only on appellants' own data from experiments with dogs. The comparison is of the combination composition according to the invention versus the additive effect of the components separately. This is the classic way of showing synergism. Appellants never alleged any comparison to Nishimura. Appellants arguments regarding Nishimura (as detailed below) pertain to the fact that it fails to suggest that its combination would provide a synergistic effect and, thus, appellants showing is unexpected in view of Nishimura.

The record is believed to make clear that the significant and practical synergistic advantage shown for appellants' combination is unexpected from the cited prior art. There are no teachings in the prior art from which one of ordinary skill in the art would expect that the combination of tiotropium and ciclesonide could provide an effect significantly greater than the additive effect of the components individually, certainly not more than twice the additive effect. The teachings of Nishimura regarding its oxitropium/beclamethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclamethasone provided only a "small improvement" in treatment; see the concluding discussion on pg. 87. Further, the title of Nishimura points only to an "additive effect" from the combination. Appellants object to the allegation in the Final Office action (page 3) that applicants admitted that Nishimura shows synergism. Appellants never made any such admission. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

It is alleged in the Final Office action (page 3, last sentence) that appellants' showing is not persuasive "because it does not show the results are greater than those expected from the prior art." Appellants strongly disagree. Appellants have shown that the 24 hour sustained bronchoprotection effect for the claimed combination was **more than twice** that of the added effect of the two components separately. This is clearly unexpected over the Nishimura teachings. From Nishimura and the other references, one of ordinary skill in the art could not have expected more than just an additive effect from a combination of

anticholinergic and steroid. Appellants show an effect more than double the additive effect. Appellants are at a loss as to how one could conclude from the cited references that such a dramatic synergistic advantage could have been expected. It is true that Nishimura teaches combining oxitropium bromide and beclomethasone (just this specific combination). But neither this teaching, nor the teachings in Banholzer and Keller, give any hint that the combination of the different anticholinergic, tiotropium, and different steroid, ciclesonide, would provide a significantly higher than additive effect. This synergistic effect is unquestionably unexpected.

Considering the record as a whole, appellants urge that they have provided clear and convincing evidence of significant and practical advantages of their particular combination. Further, they have shown that these advantages were unexpected in view of the prior art teachings. The prior art gives no hint to one of ordinary skill in the art that the specific combination of the specific anticholinergic, tiotropium salt, and the specific corticosteroid, ciclesonide, would be particularly advantageous. Thus, a clear and convincing showing of nonobviousness is provided by the showing of synergism. In view of the narrow claim scope – i.e., combination of two specific actives – the showing is also commensurate in scope with the claimed invention. Appellants urge that the showing of nonobviousness alone provides sufficient basis to reverse the obviousness rejection.

Further, appellants submit that the cited references considered as a whole fail to establish a prima facie case of obviousness or, at most, only a weak case which is readily overcome by the showing of nonobviousness in the declaration.

Nishimura discloses the use of a particular combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone diproprionate, for use in treating chronic asthma; see, e.g., the Abstract. Nishimura indicates that the combination of the oxitropium bromide provided advantages when administered in addition to beclomethasone diproprionate. But the advantages are only minor and there is no allegation or proof that the advantages are more than merely the additive effect. The title of the Nishimura article refers to only an "additive effect" from the oxitropium bromide.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts; see, e.g., col. 1, lines 15-58. Claim 5 is directed particularly to tiotropium salts.

Keller discloses adding magnesium stearate to powder formulations to improve their moisture resistance; see, e.g., col. 4, lines 16-25. Keller teaches such addition of magnesium stearate to powders containing a wide variety of active agents and includes tiotropium and

ciclesonide, separately, as examples of possible actives; see, e.g., col. 6, line 13, to col. 7, line 10. Keller also provides a general discussion of possible excipients which include some of the ones listed in the current claims; see, e.g., col. 8, lines 1-16. However, Keller provides no suggestion to specifically combine tiotropium and ciclesonide or one of the specific excipients recited in the current claims. Further, Keller certainly provides no hint that such a combination would provide unexpected synergistically advantageous properties, as shown by appellants.

The apparent basis for the rejection is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide anticholinergic of Nishimura with the tiotropium anticholinergic disclosed in Banholzer and exchange the steroid used in Nishimura with ciclesonide because it is a known steroid (as shown by Keller). Appellants disagree that the fact that Nishimura discloses a composition combining a specific anticholinergic and a steroid makes obvious any composition combining a different specific anticholinergic and different specific steroid. None of the references provide any reason for one of ordinary skill in the art to make the particular combination as claimed. Nishimura discloses a different specific anticholinergic and different steroid. It is very specific on this particular combination and gives no suggestion to exchange either of the components. Banholzer provides no teachings regarding any steroid at all with its anticholinergic. Keller provides no teaching to make any specific combination, particularly of tiotropium and ciclesonide. The combined reference teachings thus fail to meet this claim element.

The Final Office action provides no articulated reasoning with a rationale underpinning as to why one of ordinary skill in the art would have reason to make the specific combination of the claimed elements. The Final Office action provides the mere conclusory statement that the two actives were known, thus, it would be obvious to combine them. The Supreme Court has cautioned against use of this conclusory type of reasonsing to support an obviousness rejection; see, KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385, at 1396 (2007), stating: "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." As further stated in KSR "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."

The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, "a pharmaceutically acceptable excipient selected from the group

consisting of glucose, arabinose, lactose, saccharose, and maltose." None of Nishimura, Banholzer or Keller provide any teaching regarding a composition containing such a particular excipient with the particular combination of tiotropium and ciclesonide.

For these additional reasons, i.e., the weakness of the prima facie showing, the combined references in view of the evidence of nonobviousness fail to support the obviousness rejection. It is urged that the cited prior art, considered as a whole and in view o of the evidence of unexpected results, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

2b. Claim 39, on appeal, is not obvious to one of ordinary skill in the art over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura (*Allergology International*, 1999) and Banholzer (U.S. Patent No. 5,610,163) in combination; thus, the rejection under 35 U.S.C. §103 based on these references should be reversed

The additional distinction of the claims discussed in Issue **2a.** regarding the failure of the references to disclose or suggest a composition with "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose" does not apply to claim 39. However, all of the other arguments made in Issue **2a.** above apply and are incorporated by reference herein. Those arguments which apply – and which are the primary arguments for distinguishing the claimed invention – are sufficient to support the nonobviousness of claim 39. Thus, the rejection under 35 U.S.C. §103 of claim 39, on appeal, should also be reversed.

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66, on appeal, is in error and should be reversed.

The Appeal Brief fee of $540.00 is filed/paid herewith.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,
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Attorney Docket No.: 01-1174-1-C1
Date: October 4, 2010

(viii) CLAIMS APPENDIX

1. An inhalable powder pharmaceutical composition comprising:

(a) a tiotropium salt or a hydrate thereof;

(b) a steroid which is ciclesonide, and

(c) a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose,

wherein the tiotropium salt and the steroid are optionally in the form of their enantiomers, mixtures of their enantiomers, or their racemates.

3. The inhalable powder pharmaceutical composition according to claim 1, wherein the tiotropium salt is tiotropium chloride, tiotropium bromide, tiotropium iodide, tiotropium *p*-toluene sulfonate, or tiotropium methylsulfate.

4. The inhalable powder pharmaceutical composition of claim 3, wherein the tiotropium salt is tiotropium bromide.

9. The inhalable powder pharmaceutical composition according to claim 1, wherein the weight ratios of the anticholinergic to the steroid are in the range of from 1:300 to 50:1.

10. The inhalable powder pharmaceutical composition according to claim 1, wherein the weight ratios of the tiotropium salt to the steroid are in the range of from 1:250 to 40:1.

15. The inhalable powder pharmaceutical composition of claim 1, wherein the excipient has a maximum average particle size of up to 250 μm.

16. The inhalable powder pharmaceutical composition of claim 3, wherein the excipient has a maximum average particle size of up to 250 μm.

17. The inhalable powder pharmaceutical composition of claim 4, wherein the excipient has a maximum average particle size of up to 250 μm.

19. The inhalable powder pharmaceutical composition of claim 15, wherein the excipient has

a maximum average particle size of between 10 μm and 150 μm.

20. The inhalable powder pharmaceutical composition of claim 16, wherein the excipient has a maximum average particle size of between 10 μm and 150 μm.

21. The inhalable powder pharmaceutical composition of claim 17, wherein the excipient has a maximum average particle size of between 10 μm and 150 μm.

23. A capsule containing the inhalable powder pharmaceutical composition according to claim 1.

25. A capsule containing the inhalable powder pharmaceutical composition according to claim 3.

26. A capsule containing the inhalable powder pharmaceutical composition according to claim 4.

31. A capsule containing the inhalable powder pharmaceutical composition according to claim 9.

32. A capsule containing the inhalable powder pharmaceutical composition according to claim 10.

33. A capsule containing the inhalable powder pharmaceutical composition according to claim 19.

34. A capsule containing the inhalable powder pharmaceutical composition according to claim 20.

35. A capsule containing the inhalable powder pharmaceutical composition according to claim 15.

36. A capsule containing the inhalable powder pharmaceutical composition according to

claim 16.

37. A capsule containing the inhalable powder pharmaceutical composition according to claim 17.

39. A pharmaceutical composition consisting essentially of:

(a) tiotropium salt; and

(b) a steroid which is ciclesonide,

wherein the pharmaceutical composition is in the form of an inhalable powder.

63. A kit comprising one or more unit dosage containers containing an inhalable powder pharmaceutical composition comprising:

(a) a tiotropium salt or a hydrate thereof;

(b) a steroid which is ciclesonide, and

a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose,

the tiotropium salt and the steroid optionally in the form of their enantiomers, mixtures of their enantiomers, or their racemates.

64. The kit according to claim 63, further comprising instructions with directions for using the kit.

65. A kit comprising:

(a) a first container containing a first inhalable powder pharmaceutical formulation comprising a tiotropium salt and;

(b) a second container containing a second inhalable powder pharmaceutical formulation comprising a steroid which is ciclesonide,

each container further containing a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose.

66. The kit according to claim 65, further comprising instructions with directions for using the kit.

(ix) EVIDENCE APPENDIX

1. Declaration of Dr. Bouyssou under 37 C.F.R. §1.132 - Filed with Supplemental Reply of November 4, 2009, and considered and entered by the Examiner in the Office action mailed November 12, 2009 (see, e.g., pages 3-4). Copy Attached.

(x) RELATED PROCEEDINGS APPENDIX

(None)